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COVID-19 disease does not cause ovarian injury in women of reproductive period: An observational before-and-after COVID-19 study

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Abstract

Research question: Can the SARS-CoV-2 virus injure the ovaries.

Design: An observational before-and-after COVID-19 study in an Academic medical center. A total of 132 young women aged 18-40 who had the tests of reproductive function in the early follicular phase, whose information we obtained from hospital data between January 2019 and June 2021 were enrolled. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), the ratio of FSH to LH, and anti- Müllerian hormone (AMH) levels were measured for each patient both before and after COVID-19 disease.

Results: In women with unexplained infertility, the median serum AMH levels (and ranges) were 2.01 ng/mL (1.09-3.78) and 1.74 ng/mL (0.88-3.41) in the pre-COVID-19 disease and post-COVID-19 disease groups, respectively. There was no statistically significant difference in terms of serum levels of AMH between pre-and post-illness ($p = 0.097$). Serum FSH, LH, FSH/LH ratio, and E2 levels of the patients before COVID-19 illness were similar to the serum levels of the same patients after COVID-19 illness.

Conclusion: According to our study results and recent studies investigating the effect of COVID-19 on ovarian reserve, it can be suggested that the SARS-CoV-2 virus does not impact on ovarian reserve; however, menstrual status changes may be related to extreme immune response and inflammation, or psychological stress and anxiety due to the COVID-19 disease. These menstrual status changes are also not permanent and resolve within a few months following COVID-19 illness.

Keywords: COVID-19 disease, ovarian reserve, ovarian injury, reproductive function, SARS-CoV-2 virus.

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INTRODUCTION

The SARS-CoV-2 virus, called COVID-19, first appeared in Wuhan, China and rapidly spread all over the world, infecting a great deal of people. As of September 14, 2021, the number of cases was determined as 224 million and approximately 4.6 million of them died (www.who.int/emergencies/diseases/novel coronavirus-2019). As reported in recent studies, the novel virus can affect many systems of the body such as cardiovascular, musculoskeletal, nervous and reproductive systems as well as respiratory systems. Although there is a lot of research about COVID-19, there are still many unanswered questions and concerns. Undoubtedly, one of them is whether SARS-CoV-2 virus infection affects the ovarian reserve. Up to now, few studies have been published investigating the effect of COVID-19 disease on the reproductive systems. Since recent publications evaluating young women infected with COVID-19 show changes in menstrual status and reproductive hormones, it is thought that the SARS-CoV-2 virus can injure the ovaries (Ding et al., 2021, Li et al., 2021). Menstrual cycle is an important marker of reproductive function and can be influenced by many factors such as ovarian reserve, the hypothalamic-pituitary-ovarian axis (HPO), infections, psychiatric stress and medications (Rooney et al., 2018, Louis et al., 2011). Other important markers of reproductive function are follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), the ratio of FSH to LH, and anti- Müllerian hormone (AMH) (Tal et al., 2017).

AMH is a major biomarker evaluating of the ovarian follicle reserve and representing of oocyte quantity and quality (Iwase et al., 2015). AMH, belongs to transforming growth factor-β family, is secreted by granulosa cells of growing follicles which is preantral and antral follicles lesser than 8 mm (La et al., 2009, Moolhuijsen et al., 2020). AMH inhibits FSH dependent oocyte recruitment, and plays a significant act in the development of ovarian follicles (Iwase et al., 2015).

As reports to date on the impact of COVID-19 on the ovarian reserve are limited and inconsistent, we aimed to investigate whether SARS-CoV-2 virus could injure the ovaries. Therefore, we wanted to compare values of biomarkers of reproductive function of young women both before and after COVID-19 infection.

MATERIALS AND METHODS

Participants

The methodology of this study was designed as Quasi-experiment, observations and measurements were performed in Kayseri Medical Faculty of Health Sciences University. A total of 2548 young women aged 18-40 years, whose information was obtained from hospital data between January 2019 and April 2021, and who underwent reproductive function tests in the early follicular phase such as AMH, FSH, LH, E2 due to non-ovarian infertility, were included in the study. Firstly, women with ovarian disease or ovarian surgery, pregnant or lactating, chronic disorders, malignancy, use of hormonal contraceptives, use of fertility treatments (i.e. using FSH), chemotherapy or radiotherapy were excluded from the study. Additionally, 318 of them were excluded from the study since they were vaccinated for COVID-19. Secondly, the remaining participants of this study were questioned whether they had COVID-19 disease from the Ministry of Health data system. COVID-19 disease was described as a positive result by a real-time reverse-transcriptase–polymerase-chain reaction (PCR) assay of throat swab specimens (Huang et al., 2020). According to the severity of the COVID-19 disease, it was divided into mild and severe illness as specified in the American Thoracic Society/Infectious Diseases Society of America guidelines (Metlay et al., 2019).

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Eventually, after this query, it was determined that 264 participants were infected with COVID-19 disease. All positive PCR test dates of the participants were recorded. Thirdly, 117 of them were excluded from the study because the reproductive function test measurement dates belonged to the post-illness period. Remaining 190 participants were invited to our hospital by telephone to re-evaluate for tests of reproductive function 3 months after recovery from the disease. 43 of them declined to invitation. 15 of them were determined as pregnant. Finally, 132 of them accepted the invitation and the study continued with these patients. Time frames between assessments in both before and after COVID-19 disease were calculated and were recorded.

Demographic characteristics such as age, body mass index (BMI), gravida, parity, menstrual status before and after COVID-19, and medical history were obtained from the patients and saved. Further evaluation was performed for patients' menstrual status such as menstrual blood volume (according to the number of pads changed per day), duration (the number of days she had her menstruation), and menstrual period for 3 months post-COVID-19 disease. In addition it was asked whether it changed according to menstrual status pre-illness period. A menstrual irregularity was defined as patients with both shortened (<27 days) and prolonged (>35 days) menstrual period. All assessments and recordings were made by same person (ICM) objectively.

Hormones assay

Venous blood samples were obtained from each of the participants during the early follicular phase of their menstrual period. Serum AMH, FSH, LH, and E2 levels were analyzed with a human enzyme-linked immunosorbent assay (Elecsys and cobas e411 analyzers, Roche, Switzerland). All of these samples were measured in the same laboratory immediately after collection. The lowest amount of AMH that could be detected with a 95% probability in a sample was 0.01 ng/mL. A measuring of AMH range of 0.03 to 23 ng/mL supplies excellent low-level sensitivity. A measuring of E2 range of 20–4800 pg/ml, intra-assay variability 21%, a measuring of LH range of 0.2–250 mIU/ml, intra-assay variability 3.8%, a measuring of FSH range of 0.2–200 mIU/ml, intra-assay variability 3.5% were determined in the same laboratory.

Statistical analysis

All data obtained from the study participants were divided into two groups as pre- and post-COVID-19 disease and then statistically analyzed using Statistical Package for the Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA). The values were expressed as the mean ± standard deviation or n (%), median and interquartile range (IQR). We also used the log-transformed value of AMH and log (AMH) as an outcome variable.

The Student’s t-test was used to compare parametric data; the Mann–Whitney-U test was used to compare nonparametric data. Categorical data was compared using Pearson’s χ 2 tests or Fisher’s exact test. The difference among the groups was considered statistically significant when p value was less than 0.05.

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RESULTS

A total of 147 fertile women who had COVID-19 disease were evaluated for this study. Pregnancy was observed in 15 participants after COVID-19 illness and the pregnant women excluded from the study. Finally, 132 participants were further evaluated. Table 1 provides demographic characteristics of all study participants. The median age of the subjects was 28 years and the median BMI was 23.6 m^2/kg. Three of them had severe COVID-19 disease. 112 of them received antiviral treatment for covid-19. In addition, the time between the first (pre-COVID) AMH measurement and the post-COVID measurement is presented in Table 1. As the time frame between measurements seems to be quite homogeneous and short, it was not considered necessary to correct for this time difference.

Menstrual condition of the study patients in pre-COVID-19 period was compared with in post-COVID-19 period and presented in Table 2. Twelve (9.1%) of the participants before COVID-19 disease had irregular menstruation while 21 (15.9%) of them had irregular menstruation after COVID-19 disease ($p = 0.094$). The study patients had a significant reduction in menstrual volume during 3 months following illness. While there was less amount of bleeding in the menstrual period of 10 participants before COVID-19 disease, there was a decrease in the amount of bleeding in 21 participants after COVID-19 disease (7.6% vs. 15.9%, $p = 0.035$). There was no significant difference between both groups in terms of increased menstrual volume. Twelve participants had large amount of bleeding in their menstrual period in the pre-COVID-19 group and 16 of them had an increased menstrual volume in the post-illness group (9.1% vs. 12.1%, $p = 0.215$).

The serum AMH levels were compared between groups and are shown in Figure 1 and Figure 2. The median serum AMH level in participants before COVID-19 disease was 2.01 ng/mL (IQR, 1.09-3.78 ng/mL) and the median serum AMH level in participants after COVID-19 disease was 1.74 ng/mL (IQR, 0.88-3.41 ng/mL). This difference was statistically similar ($p = 0.097$**).** We also present the log-transformed value of AMH and log (AMH) as an outcome variable and compare between groups and show in Table 2 and Figure 3**.** In the early follicular phase of the study patients in the pre-COVID-19 period, FSH, LH, E2 etc. reproductive function tests were compared with the post-COVID-19 period and are presented in Table 2. There was no statistically significant difference in terms of serum levels of FSH, LH, E2 between pre-and post-illness ($p = 0.118$, $p = 0.201$, $p = 0.181$, respectively). Additionally, the ratio of FSH/LH was similar in both groups (1.42 vs.1.61, $p = 0.268$)

DISCUSSION

The SARS-CoV-2 virus has still continued to infect all over the world and there are hundreds of thousands of clinical studies on COVID-19 disease, however, it is still unclear whether COVID-19 influences on female reproductive function. Therefore, results of the present study will reduce fear and anxiety by making important contributions in this regard**.** According this study results, COVID-19 disease does not seem to injury the ovarian reserve. However, some AMH levels have decreased quite quickly. It may be caused by severity of oophoritis or multisystem inflammatory syndrome due to COVID-19.

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It is known that the most sensitive and earliest ovarian reserve biomarker is AMH (Tal et al. 2017). In this study, there was no significant difference in serum AMH levels of the patients in the pre-COVID-19 period compared to the post-COVID-19 period. In a similar study in 2021, Li et al. reported that COVID-19 illness could not change serum AMH levels among the study groups. They compared 91 women with COVID-19 of reproductive period to 91 healthy women. And also they reported that there was no significant difference for sex hormone levels such as FSH, LH, E2, progesterone, and testosterone among the study groups. Therefore they claimed that the SARS-CoV-2 virus could not affect on ovarian reserve and sex hormone levels. In the same way, in our study, serum FSH, LH, FSH/LH ratio, and E2 levels of the patients before COVID-19 illness were similar to the serum levels of the same patients after COVID-19 illness.

On the contrary, Ding et al. in 2021 reported that serum AMH levels of patients (n = 78) with COVID-19 (17 of them were severe illness) were significantly lower than serum AMH levels of healthy women (n = 51); hence, they claimed that the SARS-CoV-2 virus had a potentially harmful impact on ovarian reserve and endocrine function. They hypothesized that, the SARS-CoV-2 virus enters into the cells owing to angiotensin converting enzyme-2 (ACE2) (Hoffmann et al., 2020). In a previous animal study, it has been reported that ovarian granulosa cells have ACE2 expression (Honorato-Sampaio et al., 2012); hence, the SARS-CoV-2 virus can attack and injure on the ovary and can reduce ovarian reserve. According to our study, if this hypothesis was valid, a significant proportion of these study patients in post-COVID-19 illness would have had lower serum AMH levels. Therefore we cannot accept this hypothesis. This difference can be explained by the comparison of different groups, the different study methodology, the small number of subjects, and due to the high rate of severe covid-19 disease in their study population (17/78)(Ding et al., 2021).

In addition, recent studies were reported that, low serum AMH levels were associated with psychological stress and severity of anxiety (Yeğin et al., 2021). Menstruation, which is arranged by the HPO axis, may be easily disarranged by psychological stress, infection disease, drugs and organ dysfunctions (Yeğin et al., 2021, Kala et al., 2016). Appropriately, in our study results, it was found that the number of women with irregular menstruation and amenorrhea slightly increased after COVID-19 illness; however, the study patients had a significant reduction in menstrual volume during 3 months following illness. Nevertheless, almost all menstrual changes resolved within 3 months after the illness. In another study investigating the effect of COVID-19 on menstrual status, it was reported that menstrual volume decreased, the duration of menstrual cycles was prolonged, and amenorrhea increased (Ding et al., 2021, Li et al., 2021). Additionally, in the present study, spontaneous pregnancy was observed in 15/147 participants (10.2%) after COVID-19 illness.

Strengths and limitations

The limitations of other similar studies were taken into account and this study was designed accordingly. We aimed to evaluate the ovarian reserve after recovery; hence, serum sex hormone levels were measured at least 3 months after recovery from COVID-19 illness. As far as we know this is the first study to investigate the effect of the SARS-CoV-2 virus on the ovarian reserve, since methodology of this study was designed as Quasi-experimental. This means that ovarian reserve of women before COVID-19 disease is compared with ovarian reserve of same women after COVID-19 disease. Also this is a unique cohort, which included women within a narrow age range with two AMH measurements pre- and post-COVID. There are several limitations of our study. First, there were only 3 out of 132 women with severe COVID-19 disease due to the study population including young women; therefore, comparisons between severe and non-severe illness groups could not be performed. We could not find enough patients with severe disease, since non-menopausal women had slight severity and had better outcomes in terms of COVID-19 infection than menopausal women. Second, the limited sample size may not be sufficient for a powerful statistical analysis. Third, this study was done in single center. Fourth, since there were no serum progesterone, testosterone, and prolactin levels of all the study patients before COVID-19 illness in hospital databank, it could not be evaluated in this study. Fifth, to evaluate long term effect of the SARS-CoV-2 virus, it should be reassessed. If possible, autopsy or biopsy samples from the ovary should be evaluated to investigate the presence and long-term harm of the SARS-CoV-2 viruses in the ovary. Further researches will be needed.

Conclusions

According to our study results and recent studies investigating the effect of COVID-19 on ovarian reserve, it can be suggested that the SARS-CoV-2 virus does not impact on ovarian reserve; however, menstrual status changes may be related to extreme immune response and inflammation, or psychological stress and anxiety due to the COVID-19 disease. These menstrual status changes are also not permanent and resolve within a few months following COVID-19 illness. In addition, although menstrual irregularity was detected in more participants after COVID-19 disease, changes in the menstrual cycle were not statistically significant in our results.

Conflict of Interest Statement

All authors declare that they had no conflicts of interest associated with this study or its results.

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None

Author Contributions

ICM and YM; Study design and data analysis, manuscript writing and editing, final control and editing of the study

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ATO; data collection and final control and editing of the study

Ethics statement

This study was approved by our Clinical Research Ethics Committee, Kayseri City Education and Research Hospital (441/2021), and informed consent was obtained from all participants.

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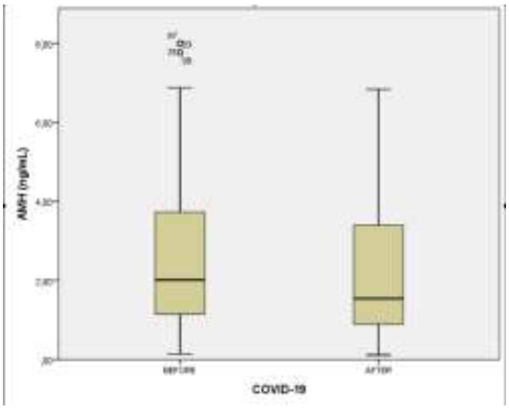

Figure 1. Boxplot of the mean serum AMH levels of participants both before and after COVID-19 disease.

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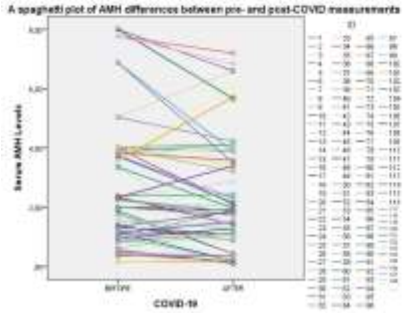

Figure 2. A spaghetti plot of serum AMH levels differences between pre- and post-COVID-19 measurements.

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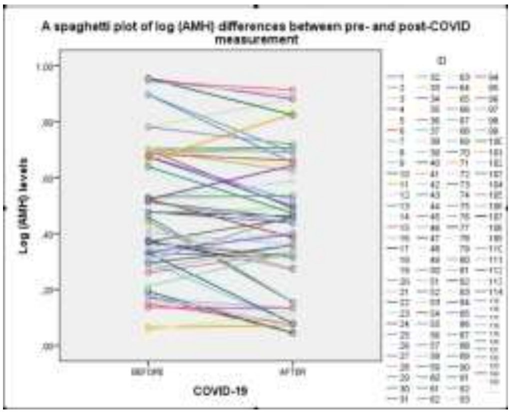

Figure 3. A spaghetti plot of Log(AMH) levels differences between pre- and post-COVID-19 measurements.

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Table 1. Demographic characteristics of the study participants.

	132 women after COVID-19 illness
Age (years)	28 (23-34)
BMI (m^2/kg)	23.6 (19.71-26.11)
Gravida	2 (2-3)
Parity	1(1-2)
Pregnancy after COVID-19 illness	15/147 (10.2%)
Antiviral treatment	112/132 (84.8%)
Smoke	7/132 (5.3%)
Severe COVID-19 disease*	3/132 (2.2%)
The time frame between assessments (mounts)	9 (7-12)
Before COVID-19 time period (mounts)	5 (4-7)
After COVID-19 time period (mounts)	4 (4-7)

BMI; body mass index, values are presented median (inter-quartile range) and n (%).

*According to the severity of the COVID-19 disease, it was divided into mild and severe illness as specified in the American Thoracic Society/Infectious Diseases Society of America guidelines (2019).

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Table 2. Comparison of the reproductive function between groups.

	Before COVID-19 disease	After COVID-19 disease	P value
Menstrual volume changes last 3 months			
Decrease in menstrual volume	10/132 (7.6%)	21/132 (15.9%)	**0.035***
Increase in menstrual volume	12/132 (9.1 %)	16 (12.1%)	0.215*
Irregular menstrual cycle	12/132 (9.1%)	21/132 (15.9%)	0.094*
AMH (ng/mL)	2.01 (1.09-3.78)	1.74 (0.88-3.41)	0.097**
Log (AMH)	**0.481 ± 0.238**	**0.435 ± 241**	**0.118****
FSH (mIU/mL)	4.91 (1.99-8.58)	5.41 (2.29-8.99)	0.118**
LH (mIU/mL)	4.14 (2.08-7.07)	4.72 (1.90-8.11)	0.201**
E2 (ng/mL)	55.42 (25.21-79.14)	58.86 (28.61-78.90)	0.181**
FSH/LH	1.42 (0.96-1.88)	1.61 (0.89-1.92)	0.268**

AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; values are presented n (%) and median (inter-quartile range) **and mean ± SD**. *Categorical data was compared using Pearson's χ 2 tests or Fisher's exact test. **The Student's t-test was used to compare parametric data; the Mann–Whitney-U test was used to compare nonparametric data.

Dr Ilknur Col Madendag is a gynaecologist at the Department of Obstetrics and Gynecology, Health Sciences University, Kayseri Medical Faculty City Hospital, Turkey. Her research focuses on ovarian endocrinology and infertility.

Key messages

Since reports to date presenting about impact of COVID-19 on the ovarian reserve are limited and inconsistent, we aimed to investigate whether SARS-CoV-2 virus could injure the ovaries. Therefore, we wanted to compare biomarkers of reproductive function of young women before COVID-19 infection with their values of same biomarkers after COVID-19 infection.

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